IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Application No. 10/586,072

Confirmation No. 7914

Applicant: Brough

Filed: July 14, 2006

TC/AU: 1632

Examiner: Wu Cheng Winston Shen

Docket No.: 253625

Customer No.: 23460

APPELLANTS' APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In support of the appeal from the final rejection dated March 24, 2010, Appellants now submit their Appeal Brief.

Real Party In Interest

The patent application that is the subject of this appeal is assigned to GenVec, Inc. and licensed by Novartis AG.

Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal.

Status of Claims

Claims 35, 39-42, 45-48, 52, and 53 are pending and are the subject of this appeal. Original claims 1-34 were cancelled, and claims 35-53 were added in the "Reply to Office Action" dated November 13, 2007. Claims 36-38, 43, 44, and 49 were cancelled in the

"Reply to Office Action" dated July 24, 2008. Claims 50 and 51 were cancelled in the "Supplemental Reply to Office Action" dated February 12, 2010.

Status of Amendments

No amendments to the claims were made subsequent to the final Office Action dated March 24, 2010.

Summary of Claimed Subject Matter

The invention is defined by all of the appealed claims; however, reference to claim 35 can be useful from the standpoint of providing a summary of the claimed subject matter. Claim 35 is the sole independent claim on appeal, and all of the other appealed claims are dependent – directly or indirectly – on claim 35.

The invention defined by appealed claim 35 relates to a method of changing the sensory perception of an animal (see specification at, e.g., page 2, lines 24-25), especially to treat hearing loss or balance disorders in the animal (see specification at, e.g., page 3, lines 24-27). The method comprises administering to the inner ear a pharmaceutical composition comprising a serotype 28 adenoviral (Ad28) vector (see specification at, e.g., page 8, lines 9-10, lines 22-25, and lines 31-40). The Ad28 vector comprises a nucleic acid sequence encoding Hath1 (see specification at, e.g., page 18, lines 7-8 and line 30) operably linked to a promoter that functions in supporting cells of the inner ear (see specification at, e.g., page 23, lines 31-34), wherein the nucleic acid sequence is expressed to produce Hath1, thereby resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear (see specification at, e.g., page 4, lines 1-3).

Issues to be Reviewed on Appeal

(a) Whether claims 35, 39, and 40 are unpatentable under 35 U.S.C. § 103(a) in view of the combination of U.S. Patent 6,838,444 (Zoghbi et al.), U.S. Patent 5,837,511 (Falck-Pedersen et al.), U.S. Patent 6,913,922 (Bout et al.), and Wigand et al. (*Arch. Virol.*, *64*(3): 225-233 (1980)).

(b) Whether claims 41 and 42 are unpatentable under 35 U.S.C. § 103(a) in view of the combination of Zoghbi et al., Falck Pedersen et al., Bout et al., Wigand et al., and U.S. Patent 6,821,775 (Kovesdi et al.).

(c) Whether claims 45-48 are unpatentable under 35 U.S.C. § 103(a) in view of the combination of Zoghbi et al., Falck Pedersen et al., Bout et al., Wigand et al., and Staecker et al. (*Otolaryngol. Head Neck Surg.*, *119*(1): 7-13 (1998)).

(d) Whether claims 52 and 53 are unpatentable under 35 U.S.C. § 103(a) in view of the combination of Zoghbi et al., Falck Pedersen et al., Bout et al., Wigand et al., U.S. Patent 6,455,314 (Wickham et al.), and Mizuguchi et al. (*Gene Ther.*, *9*(12):769-776 (2002)).

Argument

For subject matter defined by a claim to be considered obvious, the Examiner must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the appealed claims, is unobvious in view of the cited references.

a. Rejection of claims 35, 39, and 40 under 35 U.S.C. § 103(a) in view of the combination of U.S. Patent 6,838,444 (Zoghbi et al.), U.S. Patent 5,837,511 (Falck-Pedersen et al.), U.S. Patent 6,913,922 (Bout et al.), and Wigand et al. (*Arch. Virol.*, *64*(3): 225-233 (1980))

Regarding the scope and content of the prior art, Zoghbi et al. teaches a method of generating hair cells in a mammal using adenoviral vectors to deliver an atonal-associated nucleic acid.

Falck-Pedersen et al. discloses methods for generating replication-deficient non-group C adenoviral vectors (i.e., subgroups A, B, D, E, and F).

Bout et al. discloses that different adenovirus serotypes exhibit different tropisms. For example, Bout et al. discloses that adenovirus serotypes 2, 4, 5, and 7 have a natural tropism for lung epithelia and other respiratory tissues, while serotypes 40 and 41 have a natural tropism for the gastrointestinal tract. Bout et al. also discloses replication-deficient adenoviral vectors based on serotype 35 or 11, or chimeric vectors comprising a portion of the Ad35 or Ad11 genome.

Wigand et al. discloses the isolation of a serotype 36 adenovirus (Ad36), which is characterized as belonging to subgroup D. Wigand et al. discloses that Ad36 is distinct both in neutralization and hemagglutination-inhibition from all other human adenoviruses, and exhibits a unique DNA restriction pattern. Wigand et al. also discloses that the DNA structure of Ad36 is closely related to Ad28 and other subgroup D adenoviruses.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill in the art can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

The present invention, as defined by the appealed claims, is directed to a method of changing the sensory perception of an animal, which method comprises administering to the inner ear a pharmaceutical composition comprising a serotype 28 adenoviral vector (Ad28), wherein the Ad28 vector comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear. The nucleic acid sequence is expressed to produce Hath1, thereby resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Zoghbi et al. is the only cited reference that discloses a method of generating hair cells in a mammal using adenoviral vectors to deliver an atonal-associated nucleic acid. The Ad 28 vector is an adenoviral vector, and Hath-1 is an atonal-associated nucleic acid. However, while Zoghbi et al. generally refers to the use of an adenoviral vector to deliver an atonal-associated nucleic acid to inner ear cells, Zoghbi et al. does not disclose the use of an Ad28 vector to deliver Hath-1 to inner ear cells. Falck Pedersen et al. and Bout et al. disclose many adenoviral vectors, including vectors prepared from adenovirus subgroup D

adenoviruses, which includes, among many others, Ad28 and Ad36. However, Falck Pedersen et al. and Bout et al. do not disclose the use of any adenoviral vectors, let alone Ad28, to deliver any atonal-associated nucleic acid, let alone Hath-1, to inner ear cells. Similarly, Wigand et al. does not disclose the use of any adenoviral vectors to deliver any atonal-associated nucleic acid, let alone Hath-1, but rather reports on the isolation of Ad36, which is characterized as belonging to adenovirus subgroup D, and further discloses that the DNA structure of Ad28 is closely related to Ad36 and other adenoviruses of subgroup D.

In essence, the Examiner believes that the use of an Ad28 vector to deliver Hath-1 to inner ear cells to change the sensory perception of an animal (e.g., to treat hearing loss or balance disorders in an animal) would have been obvious to one of ordinary skill in the art and would have been reasonably expected to be successful because Zoghbi et al. generally discloses the use of adenoviral vectors for the same purpose, Falck Pedersen et al. discloses the preparation of vectors from various adenoviruses, Bout et al. discloses that different adenoviruses exhibit different properties, and Wigand et al. discloses Ad28.

The Examiner's position is erroneous for two reasons: (1) the Examiner has failed to make out a *prima facie* case of obviousness by providing any credible reason for one of ordinary skill in the art to have chosen, with a reasonable expectation of success, an Ad28 vector to deliver Hath-1 to change the sensory perception of an animal, and (2) the evidence of record reflects that the claimed invention exhibits unexpected properties, which would rebut a *prima facie* case of obviousness even if properly made out by the Examiner.

As the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418, 82 U.S.P.Q.2d 1385, 1396 (2007) (emphasis added)). With respect to the present application, the Examiner has failed to articulate any reasoning with a rational underpinning to support the obviousness rejection in view of the cited references.

There are at least 25 different adenoviruses that are characterized in subgroup D and at least 50 different adenoviruses in total (see, e.g., U.S. Patent No. 5,994,106 (of record)). Yet, the Examiner points to nothing in the cited references that would have provided a suitable reason for one of ordinary skill in the art to have even tried to use an Ad28 vector to deliver Hath-1 to inner ear cells to change the sensory perception of an animal, let alone

reasonably believed that an Ad28 vector could be successfully utilized to deliver Hath-1 to inner ear cells to change the sensory perception of an animal.

While adenoviruses share certain structural similarities, adenoviruses have different properties, especially as regards their abilities to infect different types of cells (i.e., different tropisms), as reported in Bout et al. As a result, one of ordinary skill in the art would not have reasonably expected all adenoviruses, or even all adenoviruses within a particular subgroup, to act in precisely the same manner. In that respect, one of ordinary skill in the art at the time of the present invention would have known that Ad36 disadvantageously infects cells of adipose tissue (see, e.g., Dhurandhar et al., *Int. J. Obes. Relat. Metab. Disord.*, *24*(8): 989-996 (2000), and Dhurandhar et al., *Int. J. Obes. Relat. Metab. Disord.*, *25*(7): 990-996 (2001)). Thus, one of ordinary skill in the art at the time of the claimed invention would have been led away from using Ad36 and other adenoviruses reported to be similar thereto, such as Ad28 as disclosed in Wigand et al., to transduce cells of the inner ear. In other words, the art available at the time of the claimed invention *taught away* from using an Ad28 vector in the method of the claimed invention. Under the circumstances, one of ordinary skill in the art would not have reasonably believed that an Ad28 vector could be successfully utilized to deliver Hath-1 to inner ear cells to change the sensory perception of an animal.

The Examiner nonetheless asserts that selecting and utilizing a particular adenovirus is a matter of "routine optimization." However, the use of a particular adenovirus to successfully provide Hath1 to generate sensory hair cells in the inner ear of an animal, especially in view of the teachings in the art at the time of the claimed invention, is nothing like the "routine optimization" of variables in a typical production process. For example, the Federal Circuit has held that differences in *concentration or temperature* will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. See *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 10 U.S.P.Q.2d 1843 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 975 (1989), and *In re Geisler*, 116 F.3d 1465, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1997). Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. See *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 U.S.P.Q. 773 (Fed. Cir. 1985). The selection of a distinct organism (i.e., an adenovirus of a particular serotype) from among a group of related but different organisms

(i.e., an adenovirus subgroup or adenoviruses in general) is much different than the routine adjustment of the conditions of a particular chemical reaction or process.

Accordingly, the Examiner has not provided a credible reason for one of ordinary skill in the art to have selected an Ad28 vector to deliver Hath-1 to inner ear cells to change the sensory perception of an animal, let alone demonstrated that one of ordinary skill in the art would have had a reasonable expectation of success in doing so. The Examiner, therefore, has failed to make out a *prima facie* case of obviousness with respect to the appealed claims.

Furthermore, even if the Examiner had properly made out a *prima facie* case of obviousness, the evidence of record reflects that the claimed invention exhibits unexpected properties, which would rebut a *prima facie* case of obviousness.

The Rule 132 declarations of Douglas E. Brough filed on February 26, 2009, and December 17, 2009, demonstrate, *inter alia*, that certain non-subgroup C adenoviral vectors, such as an Ad28 vector, unexpectedly exhibit enhanced delivery to sensory cells of the inner ear as compared to a subgroup C adenoviral vector and that this enhanced delivery is not merely the result of the non-subgroup C adenoviral vector not being a subgroup C adenoviral vector. The results described in the Rule 132 declarations were not predictable based on the disclosures of the cited references, whether considered alone or in the aggregate.

The Examiner nevertheless has characterized the results described in the Rule 132 declarations as "exactly as expected" in view of the prior art because non-subgroup C adenoviral vectors were developed to overcome technical difficulties associated with subgroup C adenoviral vectors, such as Ad5 (Office Action dated March 24, 2010, at page 21, third complete paragraph). However, the technical difficulties referred to by the Examiner and referenced in Falck-Pedersen et al. regarding the development of non-subgroup C adenoviral vectors relate to immune responses to Ad5 vectors. Whether a non-group C adenovector is more or less likely to trigger a host immune response is irrelevant to the unexpected properties of enhanced delivery to sensory cells of the inner ear as described in the Rule 132 declarations.

The Examiner also contends that the Rule 132 declarations are not persuasive because the appealed claims are not directed to non-subgroup C adenoviral vectors which transduce inner ear cells more efficiently than subgroup C vectors (see Advisory Action dated July 20, 2010). However, the appealed claims recite that the Ad28 vector "comprises a nucleic acid

sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear." Thus, the transduction of supporting cells of the inner ear is a necessary consequence of the claimed method. Indeed, expression of the nucleic acid sequence encoding Hath1 cannot occur unless such inner ear cells are transduced by the Ad28 vector containing the Hath1 sequence. While the appealed claims do not explicitly recite that an Ad28 vector transduces supporting cells of the inner ear more efficiently than subgroup C adenoviral vectors, there is no need for the claims to explicitly recite the unexpected results in order for Appellants to be able to rely on those unexpected benefits to rebut a *prima facie* case of obviousness, but rather there is only the need for the unexpected benefits to be pertinent to the claimed invention and commensurate in scope with the claims in issue, which clearly is the situation here. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987).

Considering all of the Graham factors together, it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combined disclosures of Zoghbi et al., Falck Pedersen et al., Bout et al., and Wigand et al. Accordingly, the obviousness rejection under Section 103 should be reversed.

b. Rejection of claims 41 and 42 under 35 U.S.C. § 103(a) over the combination of U.S. Patent 6,838,444 (Zoghbi et al.), U.S. Patent 5,837,511 (Falck-Pedersen et al.), U.S. Patent 6,913,922 (Bout et al.), and Wigand et al. (*Arch. Virol.*, *64*(3): 225-233 (1980), in view of U.S. Patent 6,821,775 (Kovesdi et al.)

c. Rejection of claims 45-48 under 35 U.S.C. § 103(a) in view of the combination of Zoghbi et al., Falck Pedersen et al., Bout et al., Wigand et al., and Staecker et al., *Otolaryngol. Head Neck Surg.*, *119*(1): 7-13 (1998))

d. Rejection of claims 52 and 53 under 35 U.S.C. § 103(a) in view of the combination of Zoghbi et al., Falck Pedersen et al., Bout et al., Wigand et al., U.S. Patent 6,455,314 (Wickham et al.), and Mizuguchi et al. (*Gene Ther.*, *9*(12):769-776 (2002))

Kovesdi et al. discloses an E1/E3/E4-deficient serotype 5 adenoviral vector encoding a pigment epithelium-derived factor (PEDF).

Staecker et al. discloses a method of transfecting auditory hair cells with an HSV vector encoding brain-derived neurotrophic factor.

Wickham et al. discloses recombinant adenovirus fiber proteins that are modified to reduce affinity for the CAR cellular receptor. Mizuguchi et al. discloses adenoviral vectors that are ablated for binding to CAR and αv-integrin, as well as adenoviral vectors containing the RGD peptide inserted into the HI loop of the fiber knob.

Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. do not compensate for the deficiencies of Zoghbi et al., Falck Pedersen et al., Bout et al., and Wigand et al. set forth above. In this respect, Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. do not disclose or suggest a serotype 28 adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, much less a method of using such an adenoviral vector to change the sensory perception of an animal. Therefore, each of Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. fails to provide a credible reason for one of ordinary skill in the art to utilize a serotype 28 adenoviral vector to deliver a nucleic acid sequence encoding Hath1 to the inner ear, with a reasonable expectation of success, based on the combined disclosures of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. in the manner set forth by the Office.

Conclusion

For the foregoing reasons, Appellants respectfully request that the obviousness rejections be reversed.

Respectfully submitted,

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Date: December 16, 2010

Claims Appendix

1.-34. (Cancelled)

35. (Previously Presented) A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising a serotype 28 adenoviral vector (Ad28), wherein the Ad28 adenoviral vector comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

36.-38. (Cancelled)

39. (Previously Presented) The method of claim 35, wherein the promoter is a hes-1 promoter.

40. (Previously Presented) The method of claim 35, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in at least one replication-essential gene function of the E1 region.

41. (Previously Presented) The method of claim 40, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in at least one replication-essential gene function of the E4 region.

42. (Previously Presented) The method of claim 41, wherein the adenoviral vector comprises a spacer in the E4 region.

43.-44. (Cancelled)

45. (Previously Presented) The method of claim 35, wherein the pharmaceutical composition further comprises a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent or a proliferating agent.

46. (Previously Presented) The method of claim 45, wherein the adenoviral vector comprising the nucleic acid sequence encoding Hath1 and the viral vector comprising the nucleic acid sequence encoding the neurotrophic agent or the proliferating agent are the same viral vector.

47. (Previously Presented) The method of claim 45, wherein the neurotrophic agent is a tumor growth factor, brain-derived neurotrophic factor, or nerve growth factor.

48. (Previously Presented) The method of claim 45, wherein the proliferating agent is selected from the group consisting of fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs), epidermal growth factor (EGF), E2F, and cell cycle up-regulators.

49.-51. (Cancelled)

52. (Previously Presented) The method of claim 35, wherein the adenoviral vector comprises a fiber protein ablated for binding to a coxsackie and adenovirus receptor (CAR).

53. (Previously Presented) The method of claim 35, wherein the adenoviral vector comprises a penton base protein ablated for binding to one or more integrins.

Evidence Appendix

1. Declaration under 37 C.F.R. § 1.132 of Douglas E. Brough, Ph.D., dated February 24, 2009

2. Declaration under 37 C.F.R. § 1.132 of Douglas E. Brough, Ph.D., dated December 15, 2009

Related Proceedings Appendix

Not Applicable